

A review of traditional Chinese medicine for treatment of glioblastoma

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Summary

Glioblastoma (GBM) is the most common primary malignant intracranial tumor. Due to its high morbidity, high mortality, high recurrence rate, and low cure rate, it has brought great difficulty for treatment. Although the current treatment is multimodal, including surgical resection, radiotherapy, and chemotherapy, it does not significantly improve survival time. The dismal prognosis and inevitable recurrence as well as resistance to chemoradiotherapy may be related to its highly cellular heterogeneity and multiple subclonal populations. Traditional Chinese medicine has its own unique advantages in the prevention and treatment of it. A comprehensive literature search of anti-glioblastoma active ingredients and derivatives from traditional Chinese medicine was carried out in literature published in PubMed, Scopus, Web of Science Cochrane library, CNKI, Wanfang, and VIP database. Hence, this article systematically reviews experimental research progress of some traditional Chinese medicine in treatment of glioblastoma from two aspects: strengthening vital *qi* and eliminating pathogenic *qi*. Among, strengthening vital *qi* medicine includes panax ginseng, licorice, lycium barbarum, angelica sinensis; eliminating pathogenic medicine includes salvia miltiorrhiza bunge, scutellaria baicalensis, coptis rhizoma, thunder god vine, and sophora flavescens. We found that the same active ingredient can act on different signaling pathways, such as ginsenoside Rg3 inhibited proliferation and induced apoptosis via the AKT, MEK signal pathway. Hence, this multi-target, multi-level pathway may bring on a new dawn for the treatment of glioblastoma.

Keywords: Glioblastoma (GBM), traditional Chinese medicines (TCMs), active ingredients, migration and invasion, autophagy, signal pathway

1. Introduction

Gliomas, which arise from glial or precursor cells, are the most common primary intracranial tumors. Gliomas includes diffuse astrocytic, oligodendroglial tumor, glioblastoma, ependymal tumor and so on (1,2). According to the World Health Organization (WHO) classification system, gliomas are classified into WHO grade I-IV.

Among these, WHO grade I and WHO grade II belong to low grade gliomas, WHO grade III and WHO grade IV belong to high grade gliomas. The higher the level, the higher the degree of malignancy, and the worse the prognosis. Clearly, glioblastoma (GBM), belonging to WHO grade IV, is the most frequent as well as malignant glioma in astrocytoma. In 2016, WHO according to histology combined with molecular features reclassified central nervous system (CNS) tumors, and glioblastomas were divided into glioblastoma, *IDH*-wildtype, glioblastoma, *IDH*-mutant, as well as glioblastoma, not otherwise specified (NOS) (2). Among glioblastomas, *IDH*-wildtype is mostly known as primary or de novo glioblastoma, accounting for about 90% of patients, and it is more common in elderly people over 60 years old, with poor prognosis. However, glioblastoma, *IDH*-

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mutant, known as secondary glioblastoma, is mostly evolved from low grade astrocytoma and it is more common in young people, with better prognosis, only accounting for about 10% of patients in clinic (3).

Glioblastoma has characteristics of three high and one low, namely high morbidity, high mortality, high recurrence rate, low cure rate, so the prognosis of it is very poor. According to CBTRUS statistical report in the United States in 2007-2011, it accounts for 15.4% of the primary brain tumors and 45.6% of the primary malignant brain tumors (1). The morbidity of glioblastoma is about 3.19 per 100,000 population in malignant tumors and increases with age mostly focused on 75 to 84 years, and the 5-year survival rate of patients is about 5% (1). The conventional treatment of glioblastoma is surgical resection as far as possible, followed by radiotherapy and adjuvant chemotherapy, however, its median survival is only 15 months without significant improvement (4,5). As tumor cells of glioblastoma can infiltrate into normal brain tissue, the majority of glioblastomas invariably recur despite initial treatment (6). The most advanced multimodal treatment can effectively prolong survival, however, the operation can easily cause side effects such as cerebral hemorrhage and cerebral edema, radiotherapy can cause radiation brain damage and chemotherapy can cause severe bone marrow suppression, nausea, vomiting and so on, which seriously affects patients' quality of life. The dismal prognosis and inevitable recurrence as well as resistance to chemoradiotherapy in glioblastoma may be attributed to its cellular heterogeneity and multiple subclonal populations (4). In addition, according to genomic profiling, the four glioblastoma subtypes have been defined, namely classical, mesenchymal, neural, and pro-neural and different subtypes may require different treatments (7). Hence, in order to improve the survival rate of GBM patients, it is necessary to adopt novel personalized treatment programs such as targeted therapy, immunotherapy, traditional Chinese medicine therapy and other ways. Although there are three signaling pathways (RTK/RAS/PI-3K, P53 and RB signaling) in GBM, the efficacy of related inhibitors is limited in targeted therapy of clinical trials (8). Similarly, a part of the tumor vaccines have been terminated in clinical trials of GBM immunotherapy because the effect is not obvious (9). PD-1/PD-L1 inhibitors and CTLA-4 inhibitors have been proved to effectively inhibit other tumors such as melanoma, but the role of anti-GBM is still clearly illustrated (9). Therefore, immunotherapy and targeted therapy have broad prospects in the clinical application of glioblastoma. Of course, so is traditional Chinese medicine therapy.

Traditional Chinese Medicine (TCM) has a unique and integrative theoretical system. It is a summary of the Chinese people's experience in their struggle against diseases, with a history of thousands of years. The holistic concept and syndrome differentiation are the dominant idea in clinical practice. TCM, as an important part

of complementary and alternative medicine, plays an important role in various diseases, whether used alone or in combination with western therapy. As we all known, in October 2015, Chinese scientist Tu Youyou was honored with the Nobel Prize in Physiology or Medicine because she discovered artemisinin, an extract derived from *Artemisia annua*, which can significantly and effectively treat malaria results while saving millions of lives (10). Of course, TCM has its own unique advantages in the prevention and treatment of tumors. Overall, TCM can prevent the formation of tumors, increase efficiency and reduce toxicity, reduce tumor recurrence and metastasis, prolong survival time and improve patients' quality of life (11). Without doubt, no matter a single or formulations of traditional Chinese herbs, TCM has also made great achievements in cancer. Such as, PHY906 (YIV-906), a mixture of four herbs (Astragalus, Licorice, Peony, Jujube), which was developed by Yale university professor Yungchi Cheng, and combined with chemotherapy and radiotherapy has significant effects on clinical trials of colorectal cancer, liver cancer and pancreatic cancer. In addition, Vincristine is a naturally alkaloid extracted from the leaves of *Catharanthus roseus* and it is remarkably effective in treatment of acute lymphoblastic leukemia, Hodgkin's disease and non-Hodgkin's disease, which was approved for marketing by the US FDA in 1960 (12). There are many natural anti-tumor active ingredients like this, such as paclitaxel, brucea oil, *etc.* However, at present, there are relatively few studies on traditional Chinese medicine for GBM. Therefore, this paper mainly reviews the experimental study of some traditional Chinese medicines in glioblastoma, and provides reference for its future treatment or adjuvant therapy.

2. The general principle of TCM in the treatment of GBM

As stated in Huangdi's Canon of Medicine, if the body owns sufficient vital *qi* inside, the pathogenic *qi* can't invade. The so-called "vital *qi*" is the body's resistance to the pathogenic microorganisms and the body's ability to adjust and adapt. However, "pathogenic *qi*" refers to various pathogenic factors, including wind, cold, summer-heat, dampness, dryness, heat (fire). Surely, whether the disease occurs is determined by the result of the struggle between the vital *qi* and the pathogenic *qi* in the body. If the vital *qi* is victorious, then it will not happen; however, if the pathogenic *qi* is successful, then the disease will occur, according to the theory of TCM. Therefore, strengthening vital *qi* with eliminating pathogenic *qi* is the general principle of treating diseases.

2.1. The traditional Chinese medicines against glioblastoma with strengthening vital *qi*

The most traditional Chinese medicines with the function

of strengthening vital *qi* in the body have the effect of invigorating *qi* and nourishing blood, nourishing *yin* and strengthening *yang*, in order to improve the body's immunity and resistance, expel the pathogen, and achieve the purpose of overcoming diseases and restoring health, as shown in Table 1

2.1.1. *Panax Ginseng*

Panax Ginseng has the effect of reinforcing vital energy and is known as the king of the herbs in the Orient, which originates in the dried root of the Araliaceous plant *Panax ginseng* C.A.Mey (Figure 1A) (13,14). It has gained popularity as a tonic, prophylactic and restorative agent for at least 2000 years (13). Red ginseng is a cooked product of ginseng. Its medicinal properties are warmer and better at nourishing (Figure 1B). It is reported that ginseng is contained in many active constituents such as ginsenosides, polysaccharides, alkaloids, glucosides, phenolic acid, and so on (15). Studies on ginseng have focused on ginsenosides, followed by polysaccharides. According to the positioning of sugar moieties at carbon -3 and -6, ginsenosides can be divided into protopanaxadiol (ginsenoside Rb1, Rb2, Rg3, Rc, and Rd) and pro-topanaxatriol (ginsenoside Re, Rg1, Rg2, and Rh1) groups; since carbon C-20 position substituted poorly with isobutyl, and it is further divided into 20 (S) and 20 (R) (Figures 1C-1F) (15). Modern pharmacological studies have shown that ginseng has many biological activities including anti-adhesive, anti-tumor, anti-diabetic, anti-age, neuroregulation, immunomodulation, etc (15). Studies revealed that chronic treatment with 20(s)-Rg3 induced senescence-like growth arrest in U87 glioma cells *via* AKT activation and p53/p21 signal pathway to induce reactive oxygen species (ROS) generation (16). Also, ginsenoside Rg3 inhibited growth and induced apoptosis in the U87MG cell lines, the mechanisms were related to the MEK signaling pathway and ROS (17). Additionally, ginsenoside Rd (Gs-Rd) induced apoptosis and inhibited proliferation of human glioma U251 cells by up-regulating the expression of caspase-3 and down-regulating the expression of Bcl-2 and hTERT in a dose-time-dependent manner, which may be attributed to inhibition of telomerase activity (18). The combined ginsenoside Rg3 with low-dose metronomic temozolomide displayed additive antiangiogenic effects through arresting the cell cycle and inducing apoptosis in rat C6 and human umbilical vein endothelial cells (19). Some research demonstrated that ginsenoside Rh2 exerted an anti-tumor effect on human A172 glioma cells *via* induced cell cycle arrest at G1 phase, which was related to modulating the expression of CDK4/CyclinD complex and Akt (20). Compound K, a particular ginsenoside metabolite, inhibits SDF-1-induced cells migration by down-regulating PKC α and ERK1/2 activation and changes downstream signal transduction

of the CXCR4/CXCR12 pathway (21). A new style administration has been paid more and more attention by people because of its inherent advantages, such as crossing the blood-brain barrier and sustained release. Angiopep-2 functionalized ginsenoside-Rg3 loaded nanoparticles (ANG-Rg3-NP) inhibited the proliferation of C6 glioma cells in a concentration-dependent manner and easily crossed the blood-brain barrier (22). What's more, the synergistic effect of ginsenoside-Rh2 lipid nanoparticles and borneol inhibited the proliferation of C6 glioma cells more effectively (23).

2.1.2. *Licorice*

Licorice (gancào in Chinese), is the dried root and rhizome of the *Glycyrrhiza uralensis* Fich, or *Glycyrrhiza Bat*, or *Glycyrrhiza glabra* L (Figures 1G and 1H). It was first recorded in Shennong's Herbal Classic (Shennong Bencao Jing), the oldest Chinese pharmacopoeia, with functions of tonifying the spleen, invigorating *qi*, dispelling phlegm, relieving coughing, clearing heat, detoxifying, and mediating various medicines. Licorice is widely used in clinical prescriptions of traditional Chinese medicine, even "nine out of ten prescriptions contain licorice, which is called "national elder" in China. Up to now, more than 300 flavonoids, more than 20 triterpenoids, polysaccharides, and alkaloids have been isolated from it (24). Modern pharmacological studies have shown that licorice possesses multiple biological activities such as antitumor, antiviral, anti-inflammatory, antioxidative immunoregulatory, hepatoprotective, nerve protective and other activities (25). Licochalcone A (LA) is a natural chalcone derived from licorices and its chemical structure is shown in Figure 1(I). It induced mitochondrial dysfunction in glioma stem cells to further activate mitochondrial apoptosis signaling pathways, which led to cell death *in vitro* (26). Besides, a recent study indicated that LA inhibited U87 gliomas cell growth by concurrently arresting cell cycle in the G0/G1 and G2/M phases (27). Isoliquiritigenin (ISL), a member of the flavonoids (Figure 1J) has been found to inhibit proliferation and induce differentiation of glioma stem cells *through* the Notch1 signaling pathway (28). ISL attenuated cell proliferation of U87 cells in a time and concentration dependent manner and arrested cell cycle in the S and G2/M phase. Meanwhile, ISL upregulated expression of p21 and p27 proteins, indicating that caspase mediated apoptosis was an important mechanism of ISL against glioma U87 (29). Moreover, ISL attenuated migration and invasion of SHG44 human glioma stem cells by down-regulating expression of MMP-2 and MMP-9 (30).

2.1.3. *Lycium barbarum*

Lycium barbarum, the mature fruit of *Lycium barbarum* L., is also known as wolfberry, gogi berry, and gouqizi

Table 1. Experiments and corresponding mechanisms of some TCM with strengthening vital qi acting on anti-GBM

TCM name	Tilt the Latin name	Main active compounds	Cell lines	Stages of action	Related pathway	Effects and related mechanisms	Ref.
Panax Ginseng	Ginseng Ra-dix et Rhi-zoma	20(s)-Rg3	U87	Induced senescence	AKT and p53/p21	↑p-Akt; ↑p53; ↑p21; ↑ROS;	16
		ginsenoside Rg3	U87MG	Induced apoptosis	MEK	Inhibited growth; ↑Bax; ↓Bcl-2; ↑ROS	17
		ginsenoside Rg3	C6; HUVEC	antiangiogenesis	-	arrested cycle at S phase; suppressed proliferation; ↓VEGFA; ↓Bcl-2;	19
Licorice	Glycyrrhizae Radix et Rhizoma	ginsenoside Rh2	U87MG; A172	Inhibits proliferation; induces cell cycle arrest;	Akt	arrested cycle at G1 phase; ↓CDK4; ↓CyclinD; ↓Akt; ↓p-Akt	20
		Licochalcone A	glioma stem cells	induced mitochondrial dysfunction	mitochondrial apoptotic	induced caspase-dependent cell death; Induced mitochondrial fragmentation; reduced the membrane potential; ↓ATP production	26
Lycium barbarum	Lycii Fruc-tus	Isoliquiritigenin	glioma stem cells	inhibited proliferation and induced differentiation	Notch1	↓Hes1; ↓Notch1;	28
		Isoliquiritigenin	SHG44 human glioma stem cells	inhibit migration and invasion	-	↓MMP-2; ↓MMP-9	30
		LBPs	rat C6 glioma	inhibit the growth prolong the survival regulate the blood brain barrier	-	↑CD3 ⁺ T; ↑CD8 ⁺ T; ↑TNF- α ; ↑CD4 + CD25 + Tr ↓ANXA1; ↓IL-10	34-35
Angelica sinensis	Angelicae Sinensis Radix	LBPS +TMZ	rat C6 gliomas	Inhibit growth, regulate immunity	-	↓IL-17; ↓Foxp3mRNA; ↓Treg; ↓Th17/Treg	36
		AS-C BP	DBTRG-05MG; RG2; G5T/VGH; GBM8401; GBM8901;	Inhibited proliferation, arrested cell cycle in the G0-G1 phase, induced apoptosis	p53-dependent and p53-independent pathways	Inhibited proliferation; arrested cell cycle in the G0-G1 phase; induced apoptosis; ↑p21; ↑P16; ↓p-Rb; ↑p-P53; ↑P53; ↑Bax; ↓Bcl-2; ↑caspase9; ↑caspas3; ↑Fax; ↑caspase 8	40-41
Angelica sinensis	PCH4	PCH4	DBTRG-05MG; GBM8401	Inhibited growth; induced apoptosis; reduced migrate;	JNK signaling pathway	↑p-JNK; ↑p-ERK; ↑Nur77;	42
		APs	U251	inhibited growth; inhibited proliferation; induce apoptosis	(TGF)- β	arrest cell cycle in G0/G1 phase; ↓cyclins D1, B, and E; ↓Bcl-2; ↑Bax; ↑cleaved-caspase-3; ↑E-cadherin	44

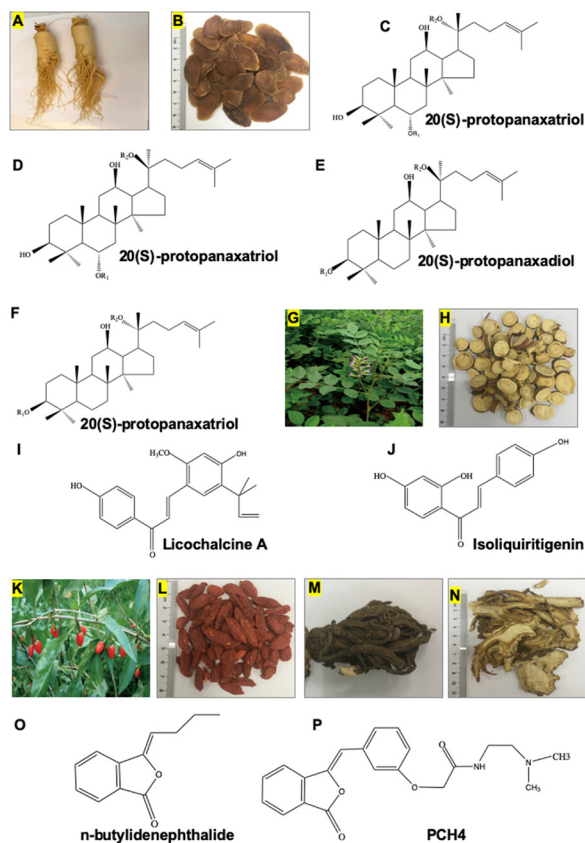


Figure 1. Some anti-GBM TCMs with activities of strengthening vital qi, including ginseng, lico-riceLycium barbarum, and Angelica sinensis, and their major active ingredients. (A) The roots of panax ginseng. (B) Chinese herbal pieces of red ginseng. (C) 20(R)-protopanaxatriol, (D) 20(S)-protopanaxatriol, (E) 20(S)-protopanaxadiol, and (F) 20(S)-protopanaxatriol, are the major active ingredients of panax ginseng. (G) The plants of licorice (91). (H) Chinese herbal pieces of licorice. (I) Licochalcine A and (J) Isoliquiritigenin are the major active ingredients of licorice. (K) The fruits of Lycium barbarum (91). (L) Chinese herbal pieces of Lycium barbarum. (M) The roots of Angelica sinensis. (N) Chinese herbal pieces of Angelica sinensis. (O) n-butylidenephthalide and (P) PCH4 are the major active ingredients of Angelica sinensis.

in Chinese (Figures 1K and 1L). It has been used in traditional homology of medicine and food for thousands of years in China. Lycium barbarum is mainly distributed in Northwest China, however lycium barbarum of the Ningxia region in China is famous for its highest quality, with an effect of nourishing liver, kidneys and eyes, and is listed in Pharmacopoeia of the People's Republic of China 2010 version (31,32). Various active compounds have been isolated from lycium barbarum, including polysaccharides, betaine, phenylpropanoids, coumarin, lignans, carotenoids, zeaxanthin dipalmitate, alkaloids, sterols, peptides, *et al* (32,33). However, Lycium barbarum polysaccharides (LBPs) accounted for 5.42-8.23% of total dried fruit and were considered the most major ingredients, while measuring the quality and pharmacological activities of lycium barbarum (31,32). It was reported that LBPs have many

biological activities, such as antiaging, neuroprotection, immunoregulatory, antioxidant, hepatoprotective, renalprotective, antidiabetic, antitoxic, and antitumor. Recent research demonstrated that LBPs inhibited the growth of tumors and prolonged the survival of rats C6 gliomas *in vivo*, which mechanism may be related to the regulation of immunity and the blood-brain barrier accompanying CD8⁺ Tcells entering the brain, exerting antitumor effects (34). This was consistent with the findings of Shan *et al.* in 2015 (35). In addition, the combination LBPs and temozolomide (TMZ) can better inhibit tumor growth compared to TMZ alone on brain glioma in rats, and this may be connected with regulation and distribution of Th17 and Treg cells (36). In short, the anti-GBM effect of LBPs may be related to immune regulation, but the specific mechanism remains unclear. In addition, there are few studies published in the English literature, and further research is needed.

2.1.4. *Angelica sinensis*

Angelica sinensis, called danggui in Chinese, is the root of *Angelica sinensis* (Oliv) Diels (Figures 1M and 1N). It is a Chinese herbal medicine with a history of more than 2000 years and a good medicine for tonifying blood (37). It can be cultivated in many provinces in China, especially in Minxian County, Gansu Province (38). According to ancient Chinese medicine records *Angelica sinensis* has the functions of tonifying blood and regulating menstruation, promoting blood circulation and relieving pain, moistening intestine and relaxing bowel. It is mainly used to treat various gynecological diseases, including dysmenorrhea, amenorrhea, irregular menstruation, menopause and postpartum blood deficiency (37,38). More than 50 constituents have been isolated from the roots of *Angelica sinensis*. However, more than 165 constituents have been isolated from the whole plant since the 1970s (38). The chemical constituents of it include volatile oil, organic acids, polysaccharides and flavonoids. According to the current Chinese Pharmacopoeia (2010 edition), *Z*-ligustilide and ferulic acid have been officially used as marker compounds to characterize the quality of *Angelica sinensis* (38). In addition, polysaccharides have also attracted widespread attention as one of its main components (39). A series of studies have confirmed that *Angelica sinensis* and its derivatives have anti-glioma effects. AS-C, a chloroform extract from it, treated with glioma cells, showed that it not only inhibited cell proliferation, arrested cell cycle in the G0-G1 phase, induced apoptosis through P53-dependent and independent pathways, but had less toxic side effects compared with the current chemotherapy drugs such as Carmustine (BCNU), Taxol, and Temozolomide (40). Moreover, further studies confirmed that n-butylidenephthalide (BP), a major component of *Angelica sinensis* chloroform extract

(Figure 1O), has the same mechanism of action against glioma as described above (41). In order to study the gene expression of BP-induced glioma cell apoptosis, studies have shown that BP increased the expression of Orphan nuclear receptor Nur77-gene, releasing Nur77 from the nucleus to the cytoplasm, releasing cytochrome C from mitochondria, and activating mitochondria-associated apoptotic pathway (42). In addition, PCH4 is one of the derivatives of BP (Figure 1P), which has four times the anti-tumor effect of BP and induces Nur77-mediated apoptosis *via* the JNK signaling pathway (43). Z-ligustilide (LIG), an essential oil extract of *Angelica siensis*, significantly reduces the migration of Human Glioblastoma T98G Cells (44). *Angelica polysaccharides* (APs) could inhibit U251 glioma cells proliferation, arrest cell cycle in G0/G1 phase, and promote apoptosis by up-regulating Bax and cleaved-caspase-3 and down-regulating Bcl-2 expression *in vitro* and *in vivo* (45).

2.2. The traditional Chinese medicines against glioblastoma with eliminating pathogenic qi

The most traditional Chinese medicines with the function of eliminating pathogenic *qi* in the body have the effect of clearing heat and removing toxins, activating blood and removing stasis, in order to directly expel the pathogen, promote blood circulation, and achieve the purpose of overcoming diseases and restoring health, as shown in Table 2.

2.2.1. *Salvia miltiorrhiza* Bunge

Salvia miltiorrhiza Bunge, also known as danshen in Chinese, derived from the dried roots and rhizomes of a *salvia* species of Lamiaceae family (Figures 2A and 2B). It was first cited in Shen Nong Ben Cao Jing and was classified as top grade goods, with the effect of promoting blood circulation to regulate menstruation, dispelling blood stasis to relieve pain, cooling blood to eliminate carbuncles, and tranquilizing mind (46). So far, there has been broad studies on the chemical constituents and pharmacological activities of it. It was found that Danshen contains more than 200 chemical constituents, which have been isolated and identified (46-48). These chemical constituents were classified into three groups according to their structures, such as lipophilic diterpenoids, hydrophilic phenolic acids and others, and the first two were considered to be the main bioactive constituents of Danshen (47,48). The lipophilic diterpenoids are mainly composed of tanshinones, including tanshinone I, tanshinone IIA, tanshinone IIB, cryptotanshinone, dihydrotanshinone *etc.* However, hydrophilic phenolic acids mainly included salvianolic acid A-E, rosmarinic acid and so on (49). Numerous studies have demonstrated its bioactivities such as anti-oxidative, anti-inflammation,

anti-atherogenesis, anti-thrombosis, anti-hypertension, anti-fibrotic, immunoregulatory, neuroprotective, anti-tumor, *etc.* Relevant literature has shown that many extracts of Danshen possess antiglioma properties. Dihydrotanshinone (Figure 2C) could effectively inhibit the proliferation of human glioma SHG-44 cells in a dose and time dependent manner and induce apoptosis *via* activation of caspase-3 and caspase-9 and promoting the release of cytochrome C, which further leads to nuclear condensation and DNA fragmentation (50). Moreover, *in vitro* Glioblastoma model experiment, dihydrotanshinone could increase the efficacy of temozolomide and reduce side effects (51). In addition, cryptotanshinone (Figure 2D) has been reported to inhibit U87 cells and T78G cells proliferation and arrest in G1/G0 phase *via* downregulating cell cycle-related proteins cyclinD1 and survivin regulated by the STAT3 signaling pathway (52). Wang *et al.* demonstrated that tanshinone IIA (Figure 2E) suppressed proliferation, induced apoptosis and differentiation in human glioma U87 cells (53). Additionally, Tang *etc.* also showed that tanshinone IIA inhibited growth and induced apoptosis in rat C6 glioma cells, which was related to the STAT3 signaling pathway (54).

2.2.2. *Scutellaria baicalensis*

Scutellaria baicalensis (*huangqin* in Chinese), is the dried root of the perennial herb Lamiaceae family *Scutellaria baicalensis* Georgi (Figures 2F and 2G). The earliest description of it was recorded in the *Shijing* of the Western Zhou Dynasty, however, *Shennong Herbal Classic*, written in the Han Dynasty, first recorded its medicinal application (55). In Chinese herbology, it exhibits functions of clearing heat, drying dampness, purging fire and detoxifying, hemostasis, and preventing miscarriage. It has been mainly used in the treatment of jaundice, dysentery, pyrexia, diarrhea, carbuncles, and infections of the respiratory and gastrointestinal tracts (56,57). So far, more than 295 compounds have been isolated from it (58). Among them, flavonoids and their glycosides including baicalein, baicalin, wogonin, wogonosides, oroxylin A, are the major compounds with anti-tumor, anti-oxidant, anti-inflammatory, anti-microbial, neuroprotective and other pharmacological activities (58,59). Some studies have shown that *Scutellaria baicalensis* and its extracts have an anti-glioma effect, which brings hope for the treatment of glioma in the future. Research by Zhang Li *et al.* showed that Wogonoside (Figure 2H) induced autophagy and promoted apoptosis on different glioma cell lines, the mechanisms of apoptosis were attributed to activation of the p38 MAPK signaling pathway, inhibition of the PI3K/AKT/mTOR/p70S6K signaling pathway and production of ROS (60). Wogonin (Figure 2I) effectively inhibited cell growth, induced cell cycle arrest at the G0/G1 phase and induced cell differentiation into mature

Table 2. Experiments and corresponding mechanisms of some TCM with eliminating pathogenic qi acting on anti-GBM

TCM name	Tilt the Latin name	Main active compounds	Cell lines	Stages of action	Related pathway	Effects and related mechanisms	Ref.
Salvia miltiorrhiza Bunge	Salviae Miltiorrhizae Radix et Rhizoma	Dihydratanshinone cryptotanshinone	SHG-44; U87MG; T98G U87; T78G	Inhibited proliferation; induced apoptosis; augment TMZ efficacy Suppress proliferation	- STAT3	↓proliferation; Induced DNA fragmentation; ↑nuclear condensation; ↑Caspase3; ↑caspase9; ↑cytochrome c; ↓proliferation; Arrested cell cycle in G1/G0 phase; ↓cyclin D1; ↓survivin; ↓p-STAT3 Tyr705; attenuated STAT3 nuclear translocation	50,51 52
Scutellaria baicalensis	Scutellariae Radix	Tanshinone IIA Wogonoside	U87 U251MG; SHG44; A172; U87MG	Inhibited proliferation; induced apoptosis; induced differentiation Induced autophagy; promoted apoptosis	- P38 MAPK; PI3K/AKT/mTOR/p70S6K;	↓proliferation; Arrested cell cycle in G1/G0 phase; ↑ADPRTL1mRNA; ↑CYP1A1; ↑GFAP; ↓nestin; Inhibited viability; induced mitochondrial apoptosis; ↓Bcl-2; ↑Bax; ↑cytochrome c; induced autophagy; ↑Beclin 1; ↑LC3-II; ↓p-p38; ↓p-AKT; ↓p-mTOR; ↓p-p70S6K; ↓p-JNK; ↑ROS	53 60
Coptis Rhizoma	Coptidis Rhizoma	wogonin baicalin	C6; U251 U87; U251	Inhibited proliferation; induced apoptosis; induced differentiation Inhibited migration and invasion	GSK-3β/catenin P38	↓proliferation; Arrested cell cycle in G1/G0 phase; ↓Cyclin D1; ↓CDK4; ↓CDK2; ↑P27; ↑GFAP; ↑GSK-3β; ↓β-catenin ↓proliferation; ↓migration; ↓invasion; ↓MMP-2; ↓MMP-9; ↑TIMP-1; ↑TIMP-2; ↓p-p38;	61 64
Coptis Rhizoma	Coptidis Rhizoma	Coptis chinensis granules berberine	U87; U251 U87; U251	Changed morphology; inhibited proliferation; intervated migration inhibits angiogenesis	STAT3 VEGF2/ERK	↓proliferation; changed morphology; ↓migration; induced G2/M arrest; induced apoptosis; ↓Total caspase3; ↑cleaved caspase 3; ↓HDAC3; ↓p-STAT3; ↓viability; ↓proliferation; ↓migration; ↑angiogenesis; ↓CD31; ↓p-VEGFR2; ↓p-ERK; ↓p-P38;	68 70
Thunder god vine	Radix et Rhizoma Tripterygii	berberine celastrol	T98G; U87; U251; SHG-44; U118; P53 U251; U87; C6	Induced autophagy; induced apoptosis; inhibited migration and invasion Inhibited proliferation; Induced autophagy; induced apoptosis	EGFR-MEK-ERK AMPK/mTOR/ULK1 ROS/JNK; AKT/mTOR	↓proliferation; ↑ROS; ↑Ca2+; ↑ER stress; mitochondrial dysfunction; ↓migration; ↓invasion; ↑p-PERK; ↑p-eIF2α; ↑GRP78/Bip; ↑CHOP/GADD135; ↓procaspase 3; ↑Bax; ↑cleaved PARP; ↑Cytochrome C; ↓Bcl-2; ↓EGFR; ↓p-RAF; ↓p-MEK; ↓p-ERK; ↑p-AMPK; ↓p-ULK1; ↑p-Becclin-1; ↓p-mTOR cell cycle arrest in G2/M phase; ↑Chk2; ↑p-Chk2; ↑cyclin B1; p-Cdc25C; ↑p-cdc2; ↑P21; ↓Cdc25c; change morphology; ↑cleaved PARP; ↑caspase3; ↑caspase9; ↑caspase 8; ↑autophagosomes; ↑LC3B; ↑Beclin-1; ↑P62; ↑ROS; ↑p-p38; ↑p-JNK; ↓p-Akt; ↓p-mTOR;	72-74 78
Sophora flavescens	Sophorae Flavescents Radix	triptolide matrine	U251; U87; C6; T98 U251; U87	induced apoptosis; inhibited migration and invasion induced apoptosis; inhibited migration and invasion	P53-independent P38 MAPK and AKT	↓proliferation; ↓Bcl-2; ↑Bax; cell cycle arrest in G0/G1 phase; ↓cyclin D1; ↓CDK6; ↓CDK4; ↓RB; change morphology; ↓migration; ↓invasion; ↓proliferation; ↓migration; ↓invasion; ↓N-cadherin; ↓EMT; ↑E-cadherin; ↓p-p38; ↓p-AKT;	79-80 86
		matrine	U251	Induced apoptosis; induced autophagy	PI3K/AKT; Wnt-β-catenin	↓Cyclin D1; ↑p53; ↑caspase3; ↑caspase9; ↓Bcl-2; ↑P62; ↑Beclin-1; ↑LC3III/LC3I; ↓circRNA-104075; ↓Wnt3a; ↓β-catenin; ↓p/t-PI3K; ↓p/t-AKT; ↓Bcl-9	87
		oxymatrine	U251	Inhibited proliferation; induced apoptosis	E G F R / P I 3 K / A K T / m T O R and STAT3	↓proliferation; arrested the cell cycle at the G0/G1 phase; ↓cyclin D1; ↓CDK6; ↓CDK4; ↓invasion; ↑caspase3; ↑Bax; ↓Bcl-2; ↓p-EGFR; ↓p-Akt; ↓p-mTOR; ↓p-STAT3	89

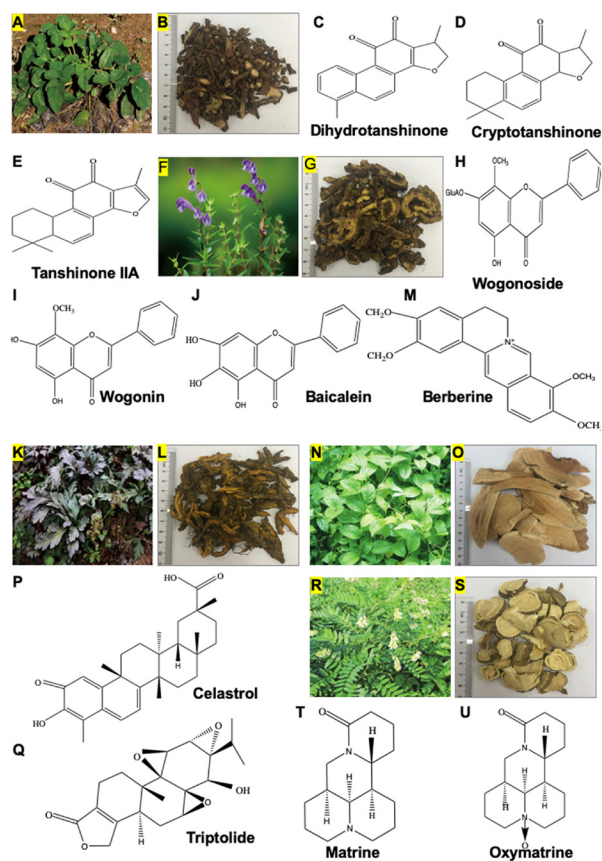


Figure 2. Some anti-GBM TCMs with activities of eliminating pathogenic qi, including *Salvia miltiorrhiza* Bunge, *Scutellaria baicalensis*, *Coptis Rhizoma*, thunder god vine, and *Sophora flavescens*, and their major active ingredients. (A) The plants of *Salvia miltiorrhiza* Bunge. (B) Chinese herbal pieces of *Salvia miltiorrhiza* Bunge. (C) Dihydrotanshinone, (D) Cryptotanshinone, and (E) Tanshinone IIA are the major active ingredients of *Salvia miltiorrhiza* Bunge. (F) The plants of *Scutellaria baicalensis*. (G) Chinese herbal pieces of *Scutellaria baicalensis*, (H) Wogonoside, (I) Wogonin, and (J) Baicalein are the major active ingredients of *Scutellaria baicalensis*. (K) The plants of *Coptis Rhizoma*. (L) Chinese herbal pieces of *Coptis Rhizoma*. (M) Berberine is one of the major active ingredients of *Coptis Rhizoma*. (N) The plants of thunder god vine plants. (O) Chinese herbal pieces of thunder god vine, (P) Celastrol and (Q) Triptolide are the major active ingredients of thunder god vine. (R) The plants of *Sophora flavescens*. (S) Chinese herbal pieces of *Sophora flavescens*. (T) Matrine and (U) Oxymatrine are the major active ingredients of *Sophora flavescens*.

astrocytes, which may be related to the inhibition of the GSK-3 β / β -catenin signaling pathway in C6 and U251 cells (61). In addition, wogonin induced growth arrest at the G1 phase, suppressed protein synthesis by activating AMPK to inhibit the mTOR pathway, induced apoptosis by activating the AMPK and p53 signaling pathways in human glioblastoma cells (62). Furthermore, it has also been reported that wogonin induced apoptosis *via* ROS generation and ER stress activation in U251 and U87 Human Glioma Cells (63). Baicalein (Figure 2J) reduced cell mobility, inhibited invasion and metastasis of U87MG and U251MG cell lines *in vitro* *via* downregulating MMP-2 and MMP-9 expression and

upregulating TIMP-1 and TIMP-2 expression through directly inhibiting the p38 signaling pathway (64).

2.2.3. *Coptis Rhizoma*

Coptis Rhizoma (CR), known as huanglian in China, is the dried rhizome of the family Ranunculaceae, which included *Coptis chinensis* Franch. (Weilian in Chinese), *Coptis deltoidea* C.Y. Cheng et Hsiao (Yalian in Chinese), or *Coptis teeta* Wall. (Yunlian in Chinese) (Figures 2K and 2L) (65,66). CR was also first mentioned in the Shen Nong Ben Cao Jing and was recorded with the effect of clearing heat, eliminating dampness, purging fire and detoxification (65,67). It is usually used to treat diarrhea, vomiting, abdominal distention, jaundice, high fever and coma, toothache, diabetes and eczema (66). Modern studies have confirmed that CR has multiple pharmacological spectrums, such as antibacterial, antiviral, anti-inflammatory, antihepatic steatosis, anti-atherosclerosis, antimyocardial ischaemia/reperfusion injury, antidiabetic, antihypertention, antihyperlipidemia, antiarrhythmia, antioxidation and antitumour effects (66). These pharmacological actions are closely related to its structure and active ingredients. So far, more than 100 components have been identified and separated from it. Among these, alkaloids are considered as the main bioactive ingredients, including berberine, palmatine, coptisine, epiberberine, jatrorrhizine and columamine (66,67). Many studies have shown that *Coptis Rhizoma* and its extract have obvious anti-glioma effects. *In vivo* and *in vitro* experiments have shown that *coptis chinensis* granules inhibited the proliferation of glioma cells, arrested cell cycle in G2/M phase and induced apoptosis *via* the down-regulation of photosynthesis of STAT3 by reducing HDAC3 (68). Berberine (Figure 2M) not only significantly inhibited inflammatory cytokine Caspase-1 activation *via* ERK1/2 signaling and subsequently decreased production of IL-1 β and IL-18 in U251 and U87 cells, but inhibited the process of EMT through upregulating the protein expression of β -catenin, α -catenin, and downregulating the protein expression of vimentin, α -SMA, so, it could effectively inhibit glioma cell proliferation, invasion and metastasis (69). Jin reported that berberine exerted the function of anti-angiogenesis in glioblastoma *via* targeting the VEGFR2/EPK pathway (70). Sun reported that berberine could inhibit mitochondrial aerobic respiration and induce oncosis-like cell death (71). Besides, berberine also was reported to induce autophagy by inhibiting the AMPK/mTOR/ULK1 pathway and induce senescence by the EGFR-MEK-ERK signaling pathway, and induce apoptosis *via* ER stress, ROS and mitochondrial-dependent pathway in glioblastoma cells (72-74).

2.2.4. Thunder God Vine

Thunder god vine (Leigongteng in Chinese) is the dried root or xylem of the root of the *Tripterygium wilfordii* hook.f. the family Celastraceae (Figures 2N and 2O). According to the records, *Tripterygium wilfordii* has the functions of dispelling wind dampness, activating blood circulation, removing swelling and pain, killing insects and detoxifying. So, it has been widely used to treat rheumatoid arthritis, nephrotic syndrome, systemic lupus erythematosus, dermatitis, eczema and so on (75). Recently, people are paying more attention to its role as an anti-tumor agent. More than 300 compounds have been identified from it, and celastrol and triptolide are the most effective bioactive components, its chemical structures are shown in Figures 2P and 2Q (75,76). Previous research has shown that Celastrol inhibits tumor growth and reduces the density of microvessels and inhibits the expression and transcription of VEGF receptors (VEGFR-1 and VEGFR-2) in nude mice human glioma xenografts (77). Recent research confirmed that celastrol inhibited proliferation, arrested cell cycle in G2/M phase, induced apoptosis and triggered autophagy in glioma cells, which was closely related to the activation of ROS/JNK signaling and the blockade of the Akt/mTOR signaling pathway (78). Of course, triptolide, another major natural compound of *Tripterygium wilfordii*, also has anti-glioma effects. Triptolide had been reported to inhibit the proliferation and invasion, and induce apoptosis of glioma cells, and enhance temozolomide-induced apoptosis and potentiate inhibition of NF- κ B signaling in glioma initiating cells (79-81).

2.2.5. *Sophora flavescens*

Sophora flavescens (kushen in Chinese) is the dried root of the Fabaceae family *Sophora flavescens* Ait., which also was first recorded in Shen Nong Ben Cao Jing (Figures 2R and 2S). It has the effect of clearing heat and dampness, killing insects and diuresis, according to the theory of traditional Chinese medicine. It is mainly used to treat dysentery, jaundice, hematochezia, eczema and other skin diseases as well as gynecopathy such as pruritus and swelling of vulva (82). It is also popular in Japan, Korea, Hawaii and other countries (83). More than 200 compounds were isolated and identified from it, among which alkaloids and flavonoids are its main active ingredients (83). Among these, matrine and oxymatrine chemical structures are as shown in Figure 2T and 2U. They are also the main biologically active ingredients and have a wide range of pharmacological effects such as antiinflammatory, antiviral, antifibrotic, antiallergic, immunoregulatory, antitumor and so on (84,85). A great amount of research has revealed that matrine and oxymatrine have anticancer activity such as lung cancer, breast cancer, liver cancer, gastric cancer, pancreatic cancer and other cancers (84). Assuredly, it also has an anti-glioma effect. Matrine could inhibit invasion and metastasis in human glioma cells *via*

regulating epithelial-to-mesenchymal transition, which may be related to the inhibition of p38 MAPK and AKT signaling (86). Matrine could induce apoptosis and autophagy in U251 cells through down-regulating circRAN-104075 and Bcl-9 expression, which is attributed to regulate the PI3K/AKT and Wnt- β -catenin pathways (87). Oxymatrine also inhibited proliferation and migration, as well as promoted apoptosis in Human Glioblastoma Cells (88). In addition, Wang *et al* further proved that Oxymatrine inhibited proliferation, arrested the cell cycle at the G0/G1 phase, induced apoptosis *via* the EGFR/PI3K/Akt/mTOR signaling pathway and STAT3 in U251MG human malignant glioma cells (89).

3. Conclusion

Glioblastoma, as a WHO grade IV glioma, is the most common primary malignant intracranial tumor. At present, conventional treatment (surgery, chemoradiotherapy) can't significantly improve the survival of patients. Hence, it is time to adopt novel personalized treatment programs such as targeted therapy, immunotherapy, gene therapy, traditional Chinese medicine therapy and other ways. Traditional Chinese medicine, as an important part of complementary and alternative medicine, the toxicity and safety of it have received increasing attention, but rational treatment and optimal application may avoid this problem (90). Traditional Chinese medicine play an important role in various diseases, whether used alone or in combination with Western therapy. Its active ingredients and derivatives have made great achievements in the treatment of diseases, such as artemisinin, vincristine, and paclitaxel, PHY906 and so on. This article studied the effects of active ingredients and derivatives about a part of traditional Chinese medicine on anti-glioblastoma, from the two aspects of strengthening vital *qi* and eliminating pathogenic *qi*. We find that the active components and derivatives of traditional Chinese medicine have functions of inhibiting proliferation, inducing cell cycle arrest, inhibiting invasion and migration, inducing apoptosis, anti-angiogenesis and improving immunity. However, since the current study is still relatively small, it is necessary to have large samples, and multicenter randomized double-blind controlled trials in the future. In addition, we also found that the same active ingredient can act on different signaling pathways. Hence, this multitarget, multi-level pathway would likely bring new directions for the treatment or adjuvant therapy of glioblastoma in the near future.

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